

# Resting Metabolic Activity in the Cingulate Cortex and Vulnerability to Posttraumatic Stress Disorder

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**Context:** Recent neuroimaging research has revealed functional abnormalities in the anterior cingulate cortex, amygdala, and hippocampus in individuals with posttraumatic stress disorder (PTSD).

**Objective:** To determine whether resting functional abnormalities found in PTSD are acquired characteristics or familial risk factors.

**Design:** Cross-sectional design including identical twins discordant for trauma exposure.

**Setting:** Academic medical center.

**Participants:** Combat-exposed veterans with PTSD (n = 14) and their identical co-twins not exposed to combat (n = 14) as well as combat-exposed veterans without PTSD (n = 19) and their identical co-twins not exposed to combat (n = 19).

**Main Outcome Measures:** We used positron emission tomography and fluorodeoxyglucose 18 to examine resting regional cerebral metabolic rate for glucose (rCMRglu).

**Results:** Veterans with PTSD and their co-twins had significantly higher resting rCMRglu in the dorsal anterior cingulate cortex/midcingulate cortex (dACC/MCC) compared with veterans without PTSD and their co-twins. Resting rCMRglu in the dACC/MCC in unexposed co-twins was positively correlated with combat exposure severity, PTSD symptom severity, and alcohol use in their exposed twins.

**Conclusions:** Enhanced resting metabolic activity in the dACC/MCC appears to represent a familial risk factor for developing PTSD after exposure to psychological trauma.

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**N**EUROIMAGING STUDIES OF posttraumatic stress disorder (PTSD) have reported functional abnormalities in several brain regions, including the anterior cingulate cortex (ACC), amygdala, and hippocampus. The ACC is a medial prefrontal structure composed of several functional subdivisions.<sup>1,2</sup> In healthy individuals, rostral regions of the ACC (rACC) are activated during emotional states and tasks that involve interference from emotional stimuli.<sup>3-8</sup> In contrast, dorsal regions of the ACC (dACC) have traditionally been thought to be involved in multiple cognitive processes like performance monitoring, response selection, error detection, and decision making,<sup>5,6,9,10</sup> though a role for the dACC in fear learning has recently been reported.<sup>11</sup> In PTSD, the rACC is hyporesponsive to trauma-related and other emotionally negative stimuli<sup>12-23</sup> and is hypoactive at rest.<sup>24</sup> In addition, rACC activation appears to be inversely related to PTSD symptom severity.<sup>19,21,25</sup> In contrast, the dACC appears to be hyperresponsive dur-

ing fear conditioning, interference, and auditory oddball tasks in PTSD.<sup>23,26-28</sup>

The amygdala is a medial temporal lobe structure that is involved in the detection of potential threat or biologically relevant predictive ambiguity in the environment.<sup>29-31</sup> In PTSD, the amygdala appears to be hyperresponsive during exposure to both trauma-related stimuli<sup>32-38</sup> and emotional stimuli unrelated to trauma,<sup>19,21,23,39</sup> during the performance of neutral tasks,<sup>24,27</sup> and even while at rest.<sup>40</sup> Amygdala activation has been shown to be positively correlated with PTSD symptom severity<sup>36,37,39,41</sup> and self-reported anxiety.<sup>34</sup>

The hippocampus is involved in explicit memory processes as well as memory for fear extinction and context in pavlovian fear conditioning.<sup>42-45</sup> Diminished hippocampal activation in PTSD has been observed during symptomatic states,<sup>12,13</sup> administration of the  $\alpha_2$ -antagonist yohimbine,<sup>46</sup> and memory tasks that involve words, passages, or spatial locations.<sup>47-50</sup>

Most functional neuroimaging studies of PTSD have involved the examination of brain activation during symptom provoca-

tion or cognitive tasks. Fewer studies have examined resting brain activity in PTSD,<sup>24,40,46,51-53</sup> and their findings have been inconsistent. Nearly all previous resting-state studies have measured regional cerebral blood flow using single-photon emission computed tomography or positron emission tomography (PET). Only 2 previous PET studies have examined regional cerebral metabolic rate for glucose (rCMRglu) at rest in PTSD. One such study reported diminished rCMRglu in the temporal cortex in PTSD.<sup>46</sup> The other study found diminished rCMRglu in cingulate gyri, hippocampus, and insula among other regions and increased rCMRglu in the cerebellum and fusiform, temporal, and occipital cortices.<sup>53</sup>

The origin of functional neuroimaging abnormalities in PTSD is largely unknown. It is tempting to conclude that because PTSD is defined as a result of a traumatic life event, all abnormalities associated with it are also caused by that event. However, PTSD is moderately heritable.<sup>54-56</sup> We studied identical twins who are discordant for combat exposure to determine whether resting rCMRglu abnormalities found in PTSD represent acquired signs of the disorder or familial risk factors for developing it upon trauma exposure. Vietnam combat veterans with and without PTSD as well as their combat-unexposed identical co-twins (without PTSD) were studied. We reasoned that resting rCMRglu abnormalities found in the combat veterans with PTSD but not in their identical co-twins would reflect acquired characteristics of PTSD, whereas resting rCMRglu abnormalities present in both the combat veterans with PTSD and their co-twins would represent familial risk factors. Based on the studies reviewed above, we hypothesized that combat veterans with PTSD would show lower rCMRglu in the rACC and hippocampus and higher rCMRglu in the dACC and amygdala compared with veterans without PTSD. However, given the dearth of informative research, we had no hypotheses regarding whether any rCMRglu abnormalities found to be associated with PTSD would represent acquired signs or risk factors. We chose to use PET over single-photon emission computed tomography owing to its superior spatial resolution. Measures of rCMRglu are closely coupled to neuronal function.<sup>57</sup>

## METHODS

### PARTICIPANTS

Participants were drawn from a pool of identical twins who had participated in a previous study of physiological responses to loud tones. A description of the recruitment strategy and characteristics of the participant population has been reported elsewhere.<sup>58</sup> Thirty-three pairs of male monozygotic twins participated (66 participants in total). Each exposed (Ex) twin had served in the Vietnam combat theater, whereas his unexposed (Ux) co-twin had not. Of the exposed twins, 14 developed current combat-related PTSD (P+) and 19 never did (P-), as determined by the Clinician-Administered PTSD Scale<sup>59</sup> using criteria from the DSM-IV.<sup>60</sup> Thus, the participants were divided into 4 different groups: (1) ExP+, combat-exposed veterans with current, combat-related PTSD (n=14); (2) UxP+, their co-twins who were not exposed to combat and did not have PTSD (n=14); (3) ExP-, combat-exposed veterans who never had combat-related PTSD (n=19); and (4) UxP-, their co-twins who

were not exposed to combat and did not have PTSD (n=19). The study was approved by the institutional review board at Partners Healthcare System, Boston, Massachusetts. Written informed consent was obtained from each participant after a full explanation of the procedures.

### DEMOGRAPHICS AND PSYCHOMETRICS

Fifty-six participants were right-handed, and 3 (1 ExP+ and 2 ExP-) were left-handed. (Handedness information was missing for 1 ExP+, 2 ExP-, 2 UxP+, and 2 UxP-.) None of the participants reported a history of major head injury involving loss of consciousness for more than 10 minutes, tumor, epilepsy, cerebrovascular accident, or other neurological disorders.

According to the Structured Clinical Interview for DSM-IV,<sup>61</sup> participants in the ExP+ group met criteria for the following current comorbid diagnoses: major depression (n=4), dysthymia (n=2), panic disorder (n=1), social phobia (n=3), specific phobia (n=1), generalized anxiety disorder (n=1), eating disorder (n=1), alcohol dependence (n=1), and substance use disorder (n=2). Participants in the other groups met criteria for the following current diagnoses: major depression (1 UxP+), dysthymia (1 ExP- and 2 UxP-), social phobia (1 UxP+), specific phobia (1 UxP+ and 1 ExP-), eating disorder (1 ExP-), and alcohol dependence (1 UxP+ and 2 UxP-).

Thirteen participants (5 ExP+, 3 UxP+, 2 ExP-, and 3 UxP-) were taking antidepressants at the time of study. Two (1 ExP+ and 1 UxP+) were taking benzodiazepines. These medications were included among the potentially confounding medications or drugs that were excluded in the subanalysis reported below. Potentially confounding drugs or medications were antihistamines, sympathomimetics, sympatholytics, parasymphomimetics, parasympholytics, skeletal muscle relaxants, hypotensive agents, vasodilating agents, pressor agents,  $\beta$ -blockers, antiarrhythmics, calcium channel blockers, narcotics, anticonvulsants, antidepressants, neuroleptics, benzodiazepines, other psychotherapeutic agents, cerebral stimulants, sedatives, and hypnotics.

Participants completed the Beck Depression Inventory,<sup>62</sup> the Michigan Alcohol Screening Test (MAST),<sup>63</sup> the Childhood Trauma Questionnaire,<sup>64</sup> the Positive and Negative Affect Schedule,<sup>65</sup> and a measure of the severity of combat exposure.<sup>66</sup> The latter scale, which has good reliability and validity, assesses the extent to which the veteran had experienced a variety of different situations in combat, including being wounded, ambushed, or captured (**Table 1**).<sup>66</sup>

### FLUORODEOXYGLUCOSE F18-PET PROCEDURES

The PET equipment and procedures have been described previously.<sup>67</sup> Participants were instructed to fast for at least 6 hours prior to PET scanning. Blood glucose levels were checked immediately before intravenous administration of fluorodeoxyglucose F18 (FDG) (approximately 185 MBq, 5 mCi). Then each participant was instructed to sit quietly with his eyes closed in a dedicated waiting room for a 40-minute uptake period. The participant was then escorted to an adjacent room that housed the HR+ PET scanner (CTI/Siemens Medical Solutions, Iselin, New Jersey), which had an in-plane and axial resolution of 4.5 mm full-width at half-maximum intensity, 63 contiguous slices with 2.5-mm separation, and a sensitivity of 200 000 cps/ $\mu$ Ci/mL (2-dimensional) and 900 000 cps/ $\mu$ Ci/mL (3-dimensional). After entering the scanner, each participant's head was fitted with an inflatable cushion to minimize movement and aligned in the scanner relative to the canthomeatal line.

**Table 1. Demographic and Clinical Characteristics of Combat-Exposed Vietnam Veterans With and Without PTSD and Their Unexposed, Identical Co-twins**

Characteristic	Mean (SD)				Mixed-Model ANOVA					
	PTSD Pairs <sup>a</sup>		Non-PTSD Pairs <sup>b</sup>		Diagnosis		Exposure		Interaction	
	Exposed (n=14)	Unexposed (n=14)	Exposed (n=19)	Unexposed (n=19)	F <sub>1,31</sub>	P Value	F <sub>1,32</sub>	P Value	F <sub>1,31</sub>	P Value
Age, y <sup>c</sup>	57.8 (2.8)		57.1 (2.2)		0.6	NS				
Education, y	14.1 (2.4)	13.5 (2.3)	14.0 (1.9)	13.4 (1.8)	0.0 <sup>d</sup>	NS	1.6 <sup>e</sup>	NS	0.0 <sup>d</sup>	NS
MAST score	9.3 (5.7)	8.4 (5.5)	6.3 (2.3)	5.6 (2.9)	4.7 <sup>f</sup>	.04	1.1 <sup>d</sup>	NS	0.00 <sup>f</sup>	NS
Combat severity score <sup>g</sup>	8.8 (2.0)		4.2 (3.0)		24.2	<.001				
CAPS score, current	66.0 (25.8)		6.6 (9.3)		86.4	<.001				
CAPS score, lifetime	90.9 (25.5)		10.6 (12.0)		145.2	<.001				
BDI score	12.2 (11.7)	2.9 (3.8)	3.1 (3.6)	4.4 (5.5)	3.7 <sup>h</sup>	NS	7.3 <sup>f</sup>	.02	12.8 <sup>h</sup>	.002
CTQ score	58.6 (8.7)	55.2 (17.8)	61.3 (8.3)	61.2 (2.9)	2.6	NS	0.5	NS	0.5	NS
PANAS score, positive affect	21.7 (7.9)	22.4 (5.4)	23.9 (8.9)	21.8 (5.7)	0.2 <sup>e</sup>	NS	0.2 <sup>i</sup>	NS	0.8 <sup>e</sup>	NS
PANAS score, negative affect	17.0 (8.7)	11.5 (2.3)	11.8 (3.4)	10.9 (1.2)	6.5 <sup>e</sup>	.02	7.4 <sup>i</sup>	.01	3.7 <sup>e</sup>	.07

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory (range, 0-63); CAPS, Clinician-Administered PTSD Scale (range, 0-136); CTQ, Childhood Trauma Questionnaire; MAST, Michigan Alcoholism Screening Test (range, 0-25); PANAS, Positive and Negative Affect Schedule; PTSD, posttraumatic stress disorder.

<sup>a</sup>The presence of current combat-related PTSD in the combat-exposed twin.

<sup>b</sup>The absence of current or past combat-related PTSD in the combat-exposed twin.

<sup>c</sup>As of January 1, 2005.

<sup>d</sup>Due to missing data, *df* = 1, 29.

<sup>e</sup>Due to missing data, *df* = 1, 30.

<sup>f</sup>Due to missing data, *df* = 1, 28.

<sup>g</sup>Eighteen-item measure (range, 0-18).

<sup>h</sup>Due to missing data, *df* = 1, 27.

<sup>i</sup>Due to missing data, *df* = 1, 31.

## MAGNETIC RESONANCE IMAGING PROCEDURES

Structural magnetic resonance imaging (MRI) scans were obtained from a Symphony/Sonata 1.5-T whole-body high-speed imaging device equipped for echo-planar imaging (Siemens Medical Systems) with a 3-axis gradient head coil. Head movement was restricted using expandable foam cushions. After an automated scout image was acquired and shimming procedures were performed to optimize field homogeneity, high-resolution structural MRI images (3-dimensional magnetization-prepared rapid gradient-echo; repetition time/echo time/flip angle = 2.73 seconds/3.31 milliseconds/7°) with a 1.33-mm slice thickness were collected. Functional MRIs were subsequently collected for separate studies, the results of which are to be reported elsewhere. The PET scans preceded MRI scans by 1 day.

## STATISTICAL ANALYSIS

Two types of analyses were used: those conducted on (1) whole-brain voxelwise FDG-PET data and (2) FDG-PET data extracted from functional regions of interest (ROIs). These 2 different types of data required somewhat different but parallel 2-factor analytic strategies. Conceptually speaking, in both types of analyses we treated exposed vs unexposed co-twins as a repeated measure (ie, exposure). The twin pairs in which the combat-exposed twin had PTSD were treated as a separate group from the twin pairs in which the exposed twin never had PTSD. We reasoned that a significant difference between these 2 groups (ie, main effect of PTSD diagnosis) would be consistent with a familial risk factor (as long as there was also no interaction between PTSD diagnosis and exposure); in this case, the combat-exposed twins with PTSD (ExP+) would have the same functional abnormality as their unexposed co-twins without PTSD (UxP+). (Follow-up analyses were conducted to confirm differences between the ExP+ and ExP- subgroups, and between the UxP+ and UxP- subgroups.) A significant PTSD di-

agnosis by exposure interaction (reflecting an abnormality in the exposed twins with PTSD only) would indicate an acquired sign of PTSD. Lastly, a difference between all combat-exposed twins compared with all twins not exposed to combat (ie, a main effect of exposure) in the absence of an interaction would suggest that a functional abnormality is associated with exposure to combat and not PTSD per se.

## Voxelwise Analysis

The whole-brain voxelwise analyses were conducted using the SPM2 software package (Wellcome Department of Cognitive Neurology, London, England). Within SPM2, each participant's PET image was coregistered to his high-resolution structural MRI. The resulting images were spatially normalized in a standard stereotactic space (Montreal Neurological Institute) and then smoothed (6 mm full-width at half-maximum). At each voxel, the rCMRglu data were normalized by the global mean and fit to a linear statistical model by the method of least squares. Hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t* statistics, which were then transformed to *z* scores.

We used an approach that consisted of 2 hierarchical levels of analysis, in which the second level's random-effects analysis absorbed the random effects from the first level. For the purpose of examining the main effect of PTSD diagnosis, for each pair, the rCMRglu values of the exposed and unexposed participants were averaged (first level), and then the pairs with and without PTSD were contrasted (second level). For the purpose of examining the PTSD diagnosis × exposure interaction, for each pair, the rCMRglu values of the exposed and unexposed participants were subtracted one from the other (first level), and then the pairs with and without PTSD were contrasted (second level). For the purpose of examining the main effect of combat exposure, the rCMRglu values of the exposed and unexposed subjects were contrasted (first level only).

**Table 2. Voxelwise Analysis Results**

Resting rCMRglu Contrasts	Region	z Score	MNI Coordinates		
			x	y	z
<b>Main Effect of Diagnosis</b>					
PTSD pairs > non-PTSD pairs	dACC	4.70	10	2	42
	Midcingulate cortex	5.03	16	-2	46
		4.65	-10	-4	38
		4.78	-46	-50	28
Non-PTSD > PTSD pairs	Left inferior parietal cortex				
	None				
<b>Within Exposed Twins</b>					
PTSD > non-PTSD	dACC	3.16	16	8	46
	Midcingulate cortex	3.49	16	-4	46
Non-PTSD > PTSD	None				
<b>Within Unexposed Twins</b>					
PTSD > non-PTSD	dACC	4.16	8	2	44
		3.54	-6	0	38
		3.35	-8	14	36
Non-PTSD > PTSD	None				

Abbreviations: dACC, dorsal anterior cingulate cortex; MNI, Montreal Neurological Institute; PTSD, posttraumatic stress disorder; rCMRglu, regional cerebral metabolic rate for glucose.

The statistical parametric maps resulting from the above voxelwise analyses were inspected for the main effect of PTSD diagnosis, main effect of exposure, and the PTSD diagnosis × exposure interaction in our a priori structures of interest (dACC, rACC, amygdala, and hippocampus). The amygdala and hippocampus were defined by their anatomical boundaries. The superior and lateral boundaries of the ACC were also defined anatomically. The dACC was defined as the portion of the anterior cingulate gyrus superior to the corpus callosum, between  $y=0$  and  $y=30$  mm.<sup>68</sup> The rACC was defined as the portion of the anterior cingulate gyrus that is anterior to the genu of the corpus callosum and where  $y>30$  mm. (Most, though not all, previous findings of diminished function in ACC in PTSD have occurred at  $y>30$  mm.) Given our strong hypotheses, we applied a significance threshold of uncorrected, 2-tailed  $P<.001$  ( $z$  score  $>3.29$ ) to rCMRglu differences found in these structures. (Because the procedure of correcting  $P$  values based on region size is biased toward finding significance in small structures, we chose to use the above stated constant significance threshold.) To regions about which we had no a priori prediction, we applied a more conservative constant significance threshold of uncorrected, 2-tailed  $P<.00001$  ( $z$  score  $>4.42$ ).

### ROI Analysis

We extracted rCMRglu data from clusters surrounding significant voxels identified in the SPM analyses. We then analyzed these clusters for the main effect of PTSD diagnosis, main effect of exposure, and their interaction using a mixed model that treated combat exposure as a within-pairs repeated measure, diagnosis as a between-pairs measure, and twin pairs as a random effect,<sup>69</sup> including the covariates described in the “Results” section. Additional correlational analyses were performed on the ROI data, as shown below.

## RESULTS

### VOXELWISE ANALYSIS

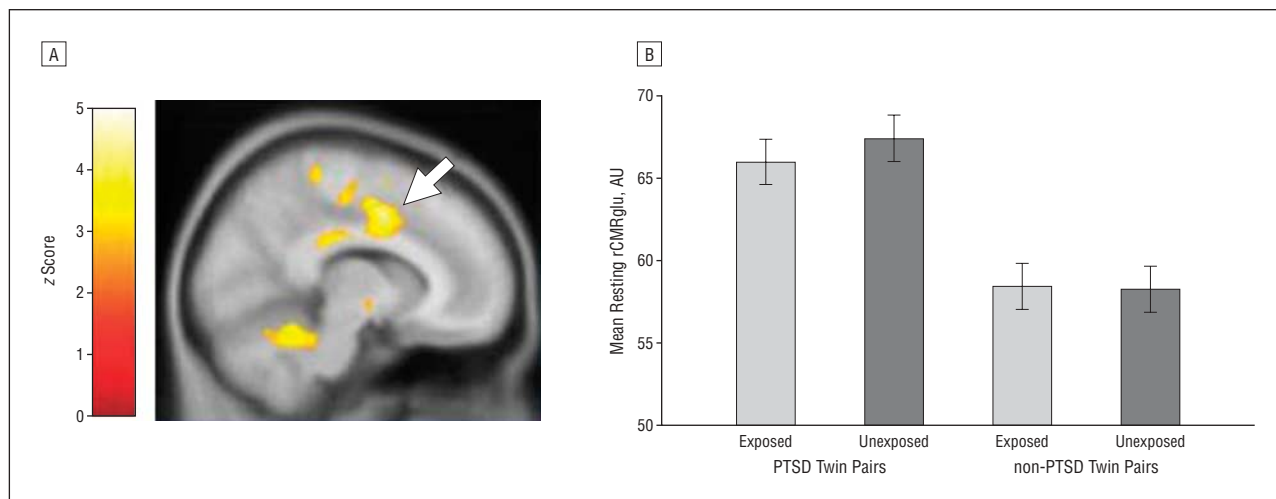
No voxels met significance thresholds for a main effect of exposure or a PTSD diagnosis × exposure interac-

tion. However, there were significant main effects of PTSD diagnosis in the dACC, midcingulate cortex, and left inferior parietal cortex (**Table 2**). In each case, combat-exposed veterans with PTSD and their unexposed co-twins (combined) exhibited greater rCMRglu than combat-exposed veterans without PTSD and their unexposed co-twins (combined). With one exception, these results remained significant when we temporarily removed from the voxelwise analyses data from (1) participants with current mood disorders or substance use disorders (all  $z$  scores  $>3.80$ ), (2) participants taking potentially confounding medications (as defined above) (all  $z$  scores  $>3.77$ ), or (3) participants who were left-handed or with missing handedness information (all  $z$  scores  $>4.41$ ). The exception was that the  $z$  score of the left inferior parietal finding dropped below threshold after these participant exclusions; for this reason, we did not consider this brain region further. No voxels exhibited significantly lower rCMRglu in the PTSD twin pairs (ie, ExP+ and UxP+ groups) relative to the non-PTSD twin pairs (ie, ExP- and UxP- groups). Comparisons between subgroups (ExP+ vs ExP- and UxP+ vs UxP-) are presented in Table 2 and are consistent with the main effect of PTSD diagnosis.

### ROI ANALYSIS

#### Dorsal Anterior Cingulate Cortex/Midcingulate Cortex

Inspection of the statistical parametric maps revealed that the most significant voxels in the dACC and midcingulate cortex (MCC) were part of a common cluster ( $k=109$  voxels), henceforth referred to as the dACC/MCC ROI (**Figure 1**). Individual subjects' values from this ROI were extracted and plotted by pairs in **Figure 2**. The within-pair correlation across PTSD and non-PTSD groups was  $r=0.73$ ,  $P<.001$ , indicating a high degree of familiarity



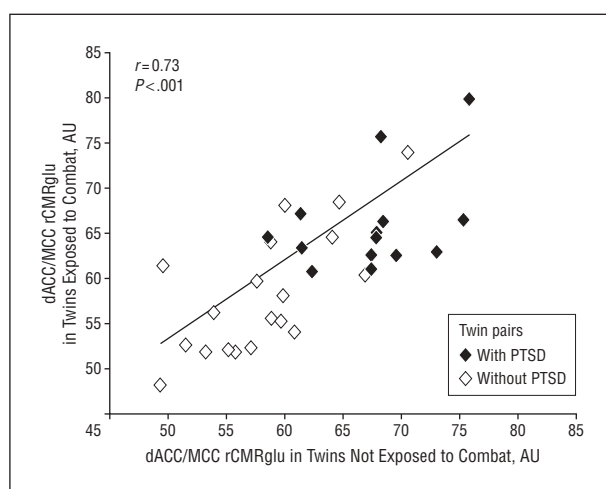
**Figure 1.** Main effect of posttraumatic stress disorder (PTSD) diagnosis on regional cerebral metabolic rate for glucose (rCMRglu). A, Resting rCMRglu in the dorsal anterior cingulate cortex/midcingulate cortex (arrow) that is greater in combat-exposed twins with PTSD and their unexposed identical co-twins compared with combat-exposed twins without PTSD and their identical co-twins. Fluorodeoxyglucose F18 data are superimposed on a standard SPM2 T1 template and displayed according to neurological convention. B, The accompanying bar graph presents group rCMRglu means. Error bars represent standard error of the mean.

of the measure (non-PTSD subjects alone,  $r=0.71$ ,  $P<.001$ ; PTSD subjects alone,  $r=0.41$ ,  $P=.07$ ; these correlations were not significantly different from each other,  $P=.25$ ).

For the dACC/MCC rCMRglu ROI, the PTSD main effect yielded  $F_{1,31,2}=18.0$ ,  $P<.001$ . The following covariates were screened as potential confounders of this result by examining their association with the dependent measure using a screening threshold of  $P<.2$ : weeks born premature, birth weight, age, total score on the Childhood Trauma Questionnaire, education, Beck Depression Inventory score, MAST score, Positive and Negative Affect Schedule scores, and severity of combat exposure (in the exposed twin). Only combat severity met this threshold. Adjusted for combat severity, the PTSD main effect yielded  $F_{1,30,4}=7.8$ ,  $P=.009$ . Parallel analyses in combat-exposed participants alone indicated that only birth weight and combat severity were potential confounders. Unadjusted, the PTSD main effect yielded  $F_{1,31}=11.5$ ,  $P=.002$  (adjusted for birth weight,  $F_{1,27}=9.2$ ,  $P=.005$ ; adjusted for combat severity,  $F_{1,30}=5.0$ ,  $P=.03$ ). Parallel analyses in participants not exposed to combat alone indicated that only MAST score and combat severity were potential confounders. Unadjusted, the PTSD main effect yielded  $F_{1,31}=28.2$ ,  $P<.001$  (adjusted for MAST score,  $F_{1,27}=28.2$ ,  $P<.001$ ; adjusted for combat severity,  $F_{1,30}=10.1$ ,  $P=.004$ ).

### Correlational Analysis With Clinical Variables

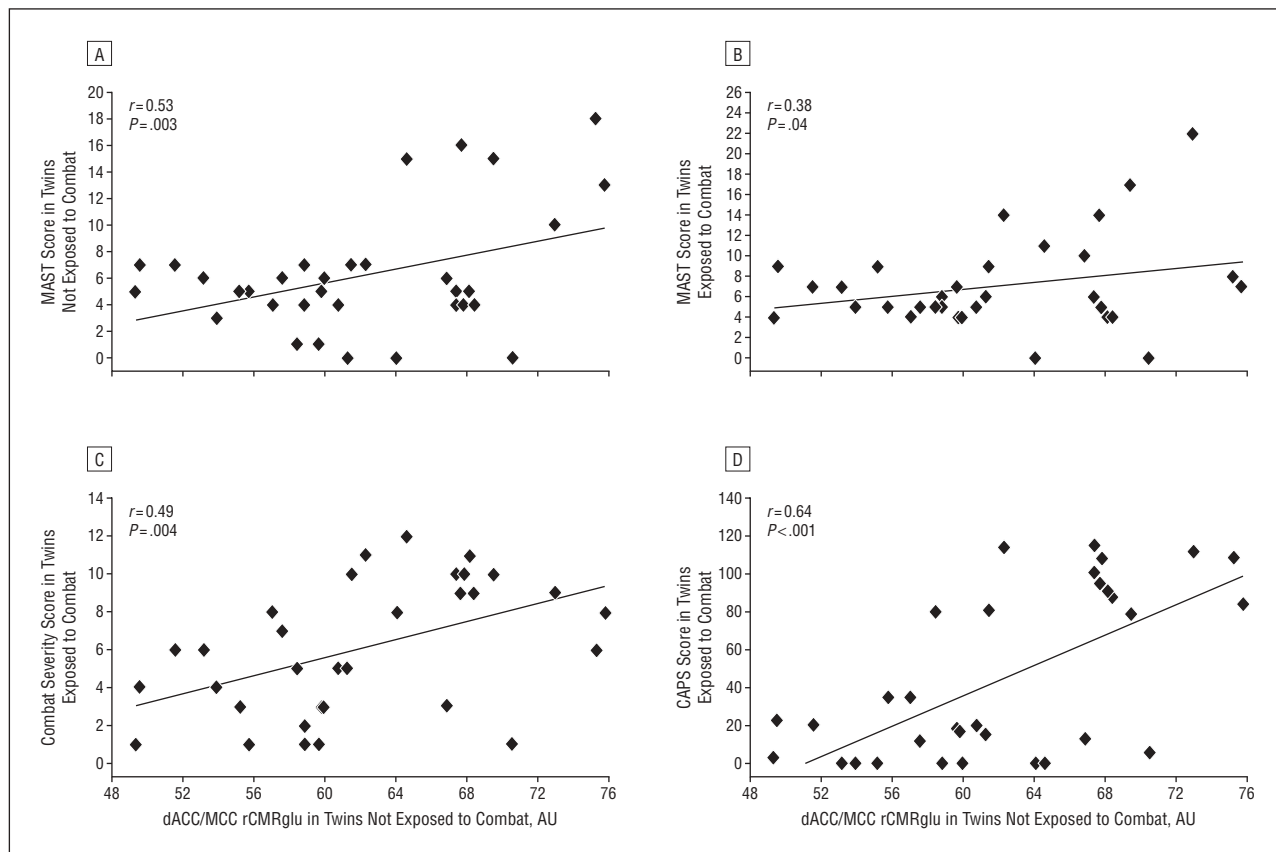
Significant correlations between dACC/MCC rCMRglu in the unexposed co-twins and other variables of interest included their own MAST scores ( $r=0.53$ ,  $P=.003$ ), their exposed twins' MAST scores ( $r=0.38$ ,  $P=.04$ ), their exposed twins' combat severity scale scores ( $r=0.49$ ,  $P=.004$ ), and their exposed twins' lifetime Clinician-Administered PTSD Scale scores ( $r=0.64$ ,  $P<.001$ ) (**Figure 3**). The last of these correlations adjusted for exposed twins' MAST and combat severity scores, which yielded partial  $r=0.53$ ,  $P=.003$ .



**Figure 2.** Correlation of regional cerebral metabolic rate for glucose (rCMRglu) between co-twins. Individual subjects' rCMRglu values from the dorsal anterior cingulate cortex/midcingulate cortex (dACC/MCC) cluster plotted by pairs.

### COMMENT

The results presented herein showed greater resting rCMRglu, indicative of greater resting metabolic activity, in the dACC/MCC of combat-exposed veterans with PTSD and their identical, combat-unexposed co-twins compared with the combat-exposed veterans without PTSD and their co-twins. This finding remained significant after adjusting for potentially confounding factors. The finding of dACC/MCC hypermetabolism in combat veterans with PTSD is consistent with previous findings of increased activation in these structures in singletons with PTSD<sup>23,26-28</sup> and further suggests that this functional abnormality may be a risk factor rather than an acquired characteristic of PTSD. The current finding appears to be inconsistent with that of a previous FDG-



**Figure 3.** Regional cerebral metabolic rates for glucose (rCMRglu) correlations with clinical variables. The scatterplots show the 0-order correlations between rCMRglu values extracted from the dorsal anterior cingulate cortex/midcingulate cortex (dACC/MCC) in co-twins not exposed to combat and their Michigan Alcoholism Screening Test (MAST) scores (A), their combat-exposed twins' MAST scores (B), their exposed twins' combat severity scores (C), and their exposed twins' lifetime Clinician-Administered PTSD Scale (CAPS) scores (D).

PET study<sup>53</sup> that reported rCMRglu decreases in the anterior cingulate in PTSD; however, because coordinates were not reported in that study, it is unclear whether those decreases occurred in rostral or dorsal portions of the anterior cingulate. One other previous FDG-PET study<sup>46</sup> reported no rCMRglu difference in the cingulate between 10 Vietnam combat veterans with PTSD and 10 healthy participants unexposed to trauma. However, unlike the current study, the previous one used a structural ROI approach, which involved extracting FDG-PET data from manually traced brain structures. The cingulate region in that study did not appear to distinguish between its different subdivisions (ie, anterior vs posterior, dACC vs rACC). Extracting and analyzing FDG-PET data from the entire cingulate gyrus could easily obscure possible group differences in specific subregions of the cingulate, such as the dACC.

We did not find evidence of resting rCMRglu main effects or interactions in the rACC, amygdala, or hippocampus. Most of the previous findings of abnormal function in these regions have occurred in neuroimaging studies that used emotional or cognitive tasks; perhaps abnormalities in these brain structures are more likely to be manifest when participants are engaged in such tasks. Furthermore, amygdala responses are known to habituate<sup>70-72</sup> for seconds to minutes, even in PTSD.<sup>19,37</sup> It is possible that such habituation occurred during the 40-minute FDG uptake period, thus obscuring any possible

group differences that may have existed early in that period. Two previous resting FDG-PET studies<sup>46,53</sup> reported no group differences between PTSD and comparison groups with regard to rCMRglu in the amygdala, though one of those studies reported diminished rCMRglu in the hippocampus.<sup>53</sup> The fact that some of our a priori brain ROIs did not show abnormal glucose metabolic rates in PTSD at rest does not preclude their involvement in the pathophysiology of the disorder. In future research, we plan to use cognitive and emotional tasks during functional MRI to further probe these structures using the present twin design.

The dACC (also referred to as the dorsal anterior midcingulate cortex<sup>2,73</sup>) appears to be involved in many cognitive processes, such as conflict monitoring, response selection, and error detection.<sup>5,10</sup> However, it also appears to be involved in aversive conditioning,<sup>11,74</sup> the anticipation and perception of pain,<sup>75,76</sup> and task/stimulus-related heart rate responses.<sup>77</sup> In rhesus monkeys, increased dACC metabolism is positively correlated with increased freezing behavior in response to a human intruder.<sup>78</sup> In humans, dACC activation is positively correlated with neuroticism and interoceptive accuracy<sup>79</sup> and emotional awareness.<sup>80</sup> Increased rCMRglu in the dACC has been reported recently in individuals with the short (s/s) allele of the serotonin transporter gene,<sup>81</sup> the frequency of which has been found to be increased in PTSD.<sup>82,83</sup>

The MAST and the measure of combat severity were originally included in the design for use as covariates to control for potentially confounding variables. Additionally, we found that hypermetabolism in the dACC/MCC in the co-twins unexposed to combat positively and significantly correlated with their own and their exposed twins' alcoholism histories as well as their exposed twins' combat exposure severity and PTSD severity. Though not predicted, these results are of substantial interest in view of a study of 4072 male-male twin pairs, both of whom were in military service during the Vietnam War, which found that the same additive genetic influences that affect the level of combat exposure also influence the level of alcohol use and the level of avoidance/arousal and reexperiencing PTSD symptoms.<sup>84</sup> The authors concluded that the genetic influences that lead to exposure to combat also lead to increased alcohol use and PTSD symptoms and further that some genetically transmitted personal characteristics, possibly including impulsivity and sensation seeking, influence the veteran's probability of being exposed to a high level of combat, PTSD symptoms, and alcohol use. The results of the present study suggest that resting dACC/MCC hypermetabolism may be an endophenotypic manifestation of these genetic influences and personality characteristics. Confidence in this conclusion, however, is limited by the lack of relevant personality measures in this twin sample as well as the dearth of prior studies regarding the relationship between dACC/MCC glucose metabolism, alcoholism, and personality characteristics such as impulsivity. However, one functional MRI study reported exaggerated dACC/MCC activation in individuals recovering from alcoholism in response to alcohol-related vs neutral pictures.<sup>85</sup> Another functional MRI study that used a perceptual face-processing task found that activation of the dACC was positively correlated with impulsivity.<sup>86</sup>

If replicated in further twin or prospective singleton studies, the current findings could have specific theoretical implications. The finding of hypermetabolism in the dACC of individuals with PTSD is consistent with conditioning and extinction neurocircuitry models of PTSD<sup>87</sup> that implicate the dACC in fear learning.<sup>11</sup> More generally, the identification of regional brain metabolic activity as a familial risk factor challenges the notion that the traumatic event is the sole etiologic factor in the development of PTSD<sup>88</sup> and is broadly consistent with many previous findings that suggest that certain psychological and biological factors appear to increase risk for PTSD following exposure to trauma.<sup>89</sup> For example, smaller hippocampal volumes,<sup>90</sup> diminished neurocognitive function,<sup>91,92</sup> and increased neurological soft signs<sup>93</sup> have been shown to be familial risk factors for the development of PTSD after psychological trauma. In contrast, diminished gray matter density in the rACC appears to be an acquired sign of PTSD.<sup>94</sup>

In summary, we found hypermetabolism in the dACC/MCC in individuals with PTSD and in their identical co-twins who were not exposed to combat and did not have PTSD. Enhanced resting metabolic activity in the dACC/MCC therefore appears to represent a familial risk factor for the development of PTSD after exposure to psy-

chological trauma. The current study is limited by the presence of disorders other than PTSD, medication use in some participants, and missing handedness data in 7 of 66 participants; however, the finding of hypermetabolism in the dACC/MCC in the P+ pairs remained even when the above participants' data were temporarily excluded from the analyses. It is important to note that, in the absence of dizygotic twin participants, the current twin design cannot distinguish between genetic and environmental contributions to familial risk. Future research examining the relationship between dACC hypermetabolism and specific genotypes should help to address this issue. Future longitudinal studies will be needed to confirm that dACC hypermetabolism increases the risk of PTSD after trauma exposure. Finally, despite the fact that PTSD and non-PTSD pairs differed significantly on rCMRglu values in the dACC/MCC, there was both variability within groups and overlap between groups. Although this pattern of findings is typical in functional neuroimaging studies of psychiatric patient groups, it limits the ability to use rCMRglu in the dACC/MCC as a sole predictor of vulnerability to PTSD following psychological trauma. In future studies, factoring in other measures (such as genotypes) may increase separation between groups and the predictive power of the rCMRglu measure.

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